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Reflections on the Anion Gap in Hyperglycemia

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THE ANION GAP is the difference between measured anions and measured cations; it reflects primarily the unmeasured anions, those not identified by the usual electrolyte determination.[1,2] An increased anion gap generally indicates the accumulation of organic anions. To calculate the gap, the following formula is often used:

$$\text{Anion gap} = [Na^+] - ([HCO_3^-] + [Cl^-]) = 8 \text{ to } 16 \text{ mEq/liter}$$

Electrolyte determination using some of the new ion-specific electrode methods may yield a slightly lower range for the anion gap but does not alter the principle.[3]

A case of a patient with hyperosmolar coma and associated electrolyte abnormalities prompted us to question how the anion gap should be calculated in such situations. Specifically, should its calculation be modified in any way to account for the dilutional effect of severe hyperglycemia on serum electrolyte levels? To our knowledge this issue has not been addressed previously in the medical literature.

To answer this question we reviewed the primary literature on the anion gap, the acid-base status in hyperglycemic coma, and the physiologic principles underlying the dilutional hyponatremia seen in severe hyperglycemia. In addition, we conducted an informal survey to determine how other house staff and faculty at our institution (Stanford [California] University Medical Center) approached this problem.

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Report of a Case

The patient, a 56-year-old woman with a history of non–insulin-dependent diabetes mellitus, presented to the hospital after being found incoherent by a relative. On arrival at the emergency department, the patient was lethargic but responsive to painful stimuli. Her blood pressure was 140/86 mm of mercury, heart rate 110 beats per minute, and respirations 24 per minute. There were blood pressure and pulse orthostatic changes. Physical examination findings were unremarkable except for a depressed mental state. Admission laboratory studies revealed the following values: serum glucose 87.4 mmol per liter (1,574 mg per dl), sodium 111 mmol per liter (mEq per liter), potassium 5.7 mmol per liter, chloride 76 mmol per liter, bicarbonate 17 mmol per liter, blood urea nitrogen 26.7 mmol per liter (74.7 mg per dl), and creatinine 177 μmol per liter (2 mg per dl). An arterial blood gas determination with the patient breathing room air showed a pH of 7.35, a $Paco_2$ of 36 torr, and a Pao_2 of 82 torr.

Before the blood gas results were received, an attempt was made to analyze her acid-base status by calculating the anion gap. The admitting house staff was unsure as to whether and how this calculation should be done given the dilutional effect of profound hyperglycemia on the serum electrolytes.

Subsequently this case was presented to 33 house officers (internal medicine residents in postgraduate years 1 to 3) and 18 general internal medicine faculty. The written report was given, and they were asked to calculate the anion gap, to give the method for their calculations, and to analyze the acid-base status.

Results

Nearly a third of the faculty (5 [28%]) and a third of the house staff (11 [33%]) significantly exaggerated the magnitude of the anion gap by correcting the sodium concentration for the degree of hyperglycemia but neglecting to correct the other electrolytes. None of the house staff and only one faculty member corrected the anion gap for the dilution of all the electrolytes. Moreover, respondents uniformly misinterpreted an increased gap as synonymous with acidosis. Only 18 house staff (54%) and 6 faculty (33%) requested a blood gas analysis to confirm this impression.

Discussion

The central issue raised by this case is whether the calculation of the anion gap should be modified to correct for the dilutional effect of severe hyperglycemia on all the serum electrolytes, as is commonly done for the serum sodium level. To our surprise, we found that medicine house staff and faculty internists at our institution frequently exaggerate the anion gap in hyperglycemia by using a "corrected" value for the serum sodium but not for other electrolytes. Using two distinct lines of reasoning, we concluded that the anion gap should be calculated from the electrolytes as measured. The basis for this conclusion will be discussed further. In addition, we detected a common misconception that an increased anion gap is indicative of acidosis. The limitations of the anion gap in leading to this conclusion warrant review.

It is commonly understood that severe hyperglycemia is associated with a dilution of the serum sodium, which resolves as the glucose level is lowered. This phenomenon was first described by Seldin and Tarail in 1949.[4] Serum electrolyte levels are diluted by the movement of water out of cells

A $AG = [Na^+] - ([Cl^-] + [HCO_3^-]) = 111$ mEq/liter $- (76$ mEq/liter $+ 17$ mEq/liter$) = 18$ mEq/liter

B $Na_c = [1.6\ (Glucose - 5.5$ mEq/liter$)] + [Na^+] = 135$ mEq/liter

C $AG_c = (Na_c/[Na^+]) \cdot AG = (135$ mEq/liter$/111$ mEq/liter$) \cdot 18 = 22$ mEq/liter

D $AG_{Nac} = Na_c^+ - ([Cl^-] + [HCO_3^-]) = 135$ mEq/liter $- 93$ mEq/liter $= 42$ mEq/liter

Figure 1.—The formulas and data used in the calculation of the anion gap (AG) in our patient are shown. Subscript "c" indicates correction for dilution by water shifting out of cells during hyperglycemia. $[Cl^-]$ = serum chloride concentration, $[HCO_3^-]$ = serum bicarbonate concentration, $[Na^+]$ = serum sodium concentration

along an osmotic gradient created by the addition of an impermeant solute such as glucose or mannitol.[5] To aid physicians in determining the degree of dehydration in severely hyperglycemic patients, it is helpful to transform or "correct" the measured serum sodium value to that which would be present after the resolution of the hyperglycemia. A commonly used correction is that for every 5.5 mmol (mEq) per liter of serum glucose greater than 5.5 mmol per liter, 1.6 mmol per liter should be added to the measured value of sodium to obtain the sodium concentration that would exist in the absence of hyperglycemia.[6] This correction factor was derived by calculating the serum glucose and sodium that would result after the addition of glucose to a hypothetical insulinopenic person. No calculations were made for other electrolytes.

Only the sodium value is typically corrected, as it is representative of the total body osmolarity and water balance. It is possible, however, that all the serum constituents are initially subject to the same dilution as the sodium.[7(p1341)]

In extremely hyperosmolal states, if the serum sodium correction alone is applied to the formula to determine the anion gap, patients will have a falsely and strikingly elevated gap (Figure 1-D). Thus, calculating the anion gap by correcting only the serum sodium value is clearly wrong.

Should the anion gap be calculated after correcting for the degree of dilution of all the electrolytes?

This question can be addressed on both practical and theoretical grounds. If it is assumed that all serum electrolyte levels are initially diluted in parallel with the sodium, the following formula derives to correct the serum chloride level, the serum bicarbonate value, and thus the anion gap (AG)[7]:

$([Na^+]$ corrected$)/([Na^+]$ measured$) \times (Cl^-, HCO_3^-,$ or AG$) =$ $(Cl^-, HCO_3^-,$ or AG$)$ corrected

This formula yields the maximal change in the anion gap that could be expected to occur before cells undergo adaptive volume-regulating increases.

With hyperglycemia (glucose levels in the range of 50 to 100 mmol per liter [900 to 1,800 mg per dl]), the corrected anion gap is increased by only 5% to 20%. Thus, in our patient, the anion gap of 18 mEq per liter would be increased to 22 mEq per liter (Figure 1-C). This small increase is unlikely to be clinically relevant. In fact, when we calculated the corrected anion gap in the only series where both the pH and the anion gap were provided, no improved discrimination of the severity of acidosis was obtained.[8] Thus, on practical grounds we would argue that this type of correction is unnecessary.

Theoretic considerations also argue against correcting the anion gap. The anion gap is not made up of a single element like sodium primarily limited to the extracellular compartment. Rather, it comprises several different ions, some of which are not limited to the extracellular compartment and whose behavior as water shifts in and out of cells is not predictable.

The exact nature of the increased anion gap in severe hyperglycemia has not been elucidated. Lactate levels are slightly elevated, but these account for only a small fraction of the gap.[8] Other contributing factors may include the hemoconcentration of albumin, renal insufficiency, mild ketosis, hyperphosphatemia, and the release of intracellular organic acids.[8,9]

As hyperglycemia resolves and water moves back into cells, some of these ions—such as phosphate and organic anions—are likely to shift back into cells and thus may not increase their extracellular concentration as does sodium. Adding to this complex situation is the fact that hypertonicity itself may alter the usual distribution and transport of ions across cell membranes. A clinical example of this is the acute hyperkalemia associated with severe hypertonicity.[10] Alterations of ion transport and the accumulation of intracellular organic ions, so-called osmolytes, allow certain cells to restore cell volume towards normal.[11-13] The net effect of these adaptive changes on serum electrolytes in human hyperosmolar coma is unknown. We do know, however, that in chronic hypotonic hyponatremic states, the sodium and chloride levels fall proportionately, whereas potassium and bicarbonate levels are maintained in the normal range.[13] Thus, at least in some chronic conditions, dilution of the sodium and chloride is not accompanied by a parallel dilution of bicarbonate. Given these considerations, we would argue on both practical and theoretic grounds that the simplest and most physiologic practice is to use the anion gap calculated from the electrolytes measured, with no correction for hyperglycemia.

Once the anion gap has been appropriately calculated, how should it be interpreted? First, it is important to emphasize that an increased anion gap is not synonymous with acidosis.[1,2,14] A study done to ascertain the diagnostic usefulness of an elevated anion gap found that only when it exceeded 30 mEq per liter was organic acidosis always identified.[14] It is not adequately appreciated that metabolic alkalosis itself is often associated with an increase in the anion gap, largely due to an increased lactate production and to increases in the concentration and negative charge on albumin.[2,8,9,15] An increased gap should simply be used to alert physicians to a possible acid-base problem and must be accompanied by measurement of the pH for proper interpretation.

The actual acid-base status of patients with hyperosmolar coma is variable. Although mild acidemia (mean pH of 7.30) is most frequently reported,[9,16] the pH was 7.35 or above in fully half the 20 patients reported by Arieff and Carroll and actually exceeded 7.42 in 5 of those.[8] The reported anion gap is also variable but tends to be elevated regardless of the pH. The mean anion gap was 34 mEq per liter in Arieff and Carroll's series and 23 mEq per liter in the patients reported by Gerich and co-workers.[8,17] Massive elevation of the anion gap, however (≥ 40 mEq per liter), was seen exclusively in patients with acidemia ($pH \leq 7.35$). Conversely, acidemia

was rarely associated with a gap of 25 mEq per liter or less.

In our particular case, the calculation of the anion gap using a corrected serum sodium value but with no correction in the serum chloride or bicarbonate levels led many house officers and faculty members to think that the patient had a massively elevated anion gap and thus severe acidosis (Figure 1). In fact, the gap of 18 mEq per liter put her in the group of patients with hyperosmolar coma who are unlikely to have clinically important acidosis.

Conclusion

The anion gap should be calculated from the serum electrolytes as measured. Correction for the dilutional effect of hyperglycemia is unnecessary on practical grounds and probably unsound on physiologic grounds. Especially to be avoided is correction of the serum sodium value alone, as this will falsely exaggerate the gap.

Although hyperglycemic coma may be associated with a high anion gap, we must emphasize that an increased gap is not synonymous with acidosis. An increased anion gap is a clinical clue that requires a pH determination (together with clinical judgment) for an accurate interpretation of a patient's acid-base status. Venous blood gas determinations may be used for this purpose.[18]

It is hoped that a clear understanding of these concepts will diminish the likelihood of a misinterpreted acid-base status with the potential for incorrect therapeutic decisions.

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Carcinocythemia

A Terminal Manifestation of Metastatic Breast Cancer

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THE SPREAD OF solid tumor cells through the circulatory system, with the documentation of such spread on a routine Wright-Giemsa stain of peripheral blood smears, is an infrequent phenomenon.[1,2(p418)] In 1960 Finkel and Tishkoff noted blast cells in the peripheral smear of a 44-year-old woman with oat cell cancer of the lung.[3] Carey and co-workers were the first to use the term "carcinocythemia" to describe this phenomenon.[4] They noted a unique population of cells on a Wright's-stained blood smear of a patient with metastatic breast cancer. Histochemical stains were used to contrast these cells from those of a second patient with breast cancer in whom acute myelocytic leukemia developed as a late complication of chemotherapy and radiation therapy that she received for her cancer. I report a rare case of a patient with advanced breast cancer in whom carcinocythemia developed in the terminal phase of her illness.

Report of a Case

The patient, a 62-year-old woman, was admitted to Virginia Mason Medical Center (Seattle, Washington) in February 1991 because she had progressive shortness of breath and lethargy. Ten years earlier she underwent a right modified radical mastectomy for infiltrating ductal carcinoma. She received adjuvant chemotherapy consisting of cyclophosphamide, methotrexate, and fluorouracil. Three years later carcinoma in situ of the left breast developed, and she underwent a left modified radical mastectomy. A year later she had a left chest wall recurrence and was treated with doxorubicin-based chemotherapy followed by radiotherapy and tamoxifen therapy. In 1988 a biopsy again showed left-sided chest wall recurrence. Despite chest wall reconstruction, photon and electron radiation therapy, and subsequent chemotherapy—fluorouracil with leucovorin calcium modulation, mitoxantrone hydrochloride, cisplatin, and vinblastine sulfate—her tumor enlarged. In June 1990, she was placed on a regimen of aminoglutethimide, but six months later left chest skin biopsies confirmed the presence of progressive adenocarcinoma. The following week, she complained of shortness of breath and difficulty concentrating.

On admission the patient was confused, but the findings of a neurologic examination were nonfocal. Left supraclavicular adenopathy and subcutaneous left chest wall nodules were noted. Her hemoglobin level was 161 grams per liter, platelet count 100×10^9 per liter (100,000 per μl), and leukocyte count 13.9×10^9 per liter (13,900 per μl). The differential leukocyte count disclosed 0.42 lymphocytes, 0.09 bands, 0.33 segmented neutrophils, 0.11 monocytes, and 0.05 metamyelocytes. A blood gas determination with the patient

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